Systematic Review and Meta-Analysis

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Liposomal bupivacaine versus traditional bupivacaine for pain control after total hip arthroplasty

A meta-analysis

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Abstract

Background: In the past, the efficacy of local infiltration of liposomal bupivacaine for total hip arthroplasty (THA) patients was in debate. Therefore, this meta-analysis was conducted to determine whether local infiltration of liposomal bupivacaine provides better pain relief after THA.

Methods: We searched Web of Science, PubMed, Embase, and the Cochrane Library databases to the April 2017. Any studies comparing liposomal bupivacaine and traditional bupivacaine were included in our meta-analysis. The outcomes included visual analog scale (VAS) at 24, 48, and 72 hours, total morphine consumption at 24 hours, and the length of hospital stay. We assessed the pooled data using a random-effect model.

Results: Six studies were finally included in this meta-analysis. Our pooled data analysis demonstrated that liposomal bupivacaine was more effective than the traditional bupivacaine in terms of VAS at 24 hours ($P = .018$) and the length of hospital stay ($P = .000$). There was no significant difference in terms of the VAS at 48 and 72 hours and total morphine consumption at 24 hours ($P > .05$).

Conclusion: Compared with the traditional bupivacaine, liposomal bupivacaine shows better pain control at 24 hours and reduces the length of hospital stay after THA. Its economic costs must be assessed in multimodal center randomized controlled trials when being recommended as a long-acting alternative analgesic agent for a THA patient.

Abbreviations: CCTs = controlled clinical trials, CI = confidence interval, MINORS = methodological index for nonrandomized studies, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCS = retrospective controlled studies, RCTs = randomized controlled trials, SD = standard deviation, THA = total hip arthroplasty, TKA = total knee arthroplasty, VAS = visual analog scale, WMD = weight mean difference.

Keywords: liposomal bupivacaine, meta-analysis, total hip arthroplasty

1. Introduction

Total hip arthroplasty (THA) is a highly effective procedure for patients who have end-stage degenerative joint disease of the hip.[1,2] It was reported that over 300,000 THAs are being performed each year in the USA.[3] It is likely that the burden of inadequate postsurgical pain management associated with these procedures will also escalate. Currently, there is no gold standard for effective management of postsurgical pain after THA.[4] Multimodal analgesia following THA has been shown to improve patient satisfaction and reduce the length of hospital stay and relevant complications.[5,6] A meta-analysis has shown that the use of local infiltration is effective for postoperative pain management in total knee arthroplasty (TKA) patients.[7] A comparison with a peripheral nerve block, local infiltration of anesthesia was easy to perform with no weakening of the muscular strength of lower limbs.[8] However, the utility of traditional local anesthetic formulations has been limited by their short duration of action.[9,10] Liposomal bupivacaine (EXPAREL) is a prolonged-release formulation of bupivacaine indicated for single-dose administration into the surgical site to produce postsurgical analgesia.[11,12] Several studies have suggested that liposomal bupivacaine significantly alleviates pain and improves quality outcomes in THA patients.[3] Other studies have drawn an opposite conclusion that liposomal bupivacaine has similar pain control efficacy while increasing the costs for THA patients.[13] In addition to the above disputes, it should be noted that the sample size of these studies was limited, which may affect the accuracy of relevant conclusions. The aim of this systematic review and meta-analysis was to investigate the evidence of local infiltration of liposomal bupivacaine versus traditional bupivacaine for pain control after THA.

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The authors have no conflicts of interest to disclose.

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2. Materials and methods

This meta-analysis was conducted in compliance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions[14] and was written following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) checklist.[15] No ethical approval and patient informed consent are required in this meta-analysis, because all analyses were based on previous published studies.

2.1. Search strategy

Two independent reviewers identified randomized controlled trials (RCTs), controlled clinical trials (CCTs), cohort studies, and retrospective controlled studies (RCS) by searching electronic databases, including Web of Science, PubMed, Embase, and Cochrane Library up to April 2017. A structured search was performed using the following search string: "liposomal bupivacaine" OR "liposome bupivacaine" OR "EXPAREL" AND ("THA" OR "THR" OR "total hip replacement" OR "total hip arthroplasty" OR "Arthroplasty, Replacement, Hip [Mesh]"). There were no language and publication restrictions.

2.2. Inclusion criteria and exclusion criteria

Studies were considered eligible for meta-analysis if they met the PICOS (population, intervention, comparator, outcome, and study design) criteria. Population: patients were scheduled for THA. Intervention: liposomal bupivacaine adjunct to local infiltration anesthesia. Comparison: traditional bupivacaine adjunct to local infiltration anesthesia. Outcomes: visual analog scale (VAS) at 24, 48, and 72 hours, total morphine consumption at 24 hours, and length of hospital stay. Study design: RCTs, CCTs, cohort studies, and RCS. Exclusion criteria: combined with other anesthesia technique for pain control; without above outcomes; duplicate publication; and editorials, comments, case reports, and conference.

2.3. Data extraction

A standard data extraction form was designed to extract the relevant data from the included studies and recorded into the Microsoft Excel (Microsoft Corporation, Redmond, WA). Two reviewers used this form to collect the information from studies independently. The extracted data from studies included author, publication year, study design, sample size of liposomal bupivacaine group and control group, age, female patients, dosage of bupivacaine, outcomes, and follow up.

The primary outcome contained a VAS with 11 pain levels (0 = no pain, 10 = extreme pain). The secondary outcome included the total morphine consumption at 24 hours. Any disagreement was resolved by discussion. For the missing data, we contacted the corresponding authors by E-mail of telephone to ensure that the information integrated. Data in other forms (i.e., median, interquartile range, and mean ± 95% confidence interval (CI)) were converted to the mean ± standard deviation (SD) according to the Cochrane Handbook.[16]

2.4. Quality assessment

For RCTs, the risk of bias was evaluated by 2 reviewers on the basis of the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0 (http://handbook.cochrane.org/).[16] A total of 7 domains were used to assess the overall quality: random sequence generation, allocation concealment, blinding of participant and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each domain was measured as low bias, unclear bias, or high bias.

We used the Methodological Index for Non-Randomized Studies (MINORS) scale to assess the quality of non-RCTs.[17] A total of 12 items were assessed and each items ranging from 0 to 2 (0 = low quality and 24 = high quality).

2.5. Outcome measures and statistical analysis

Continuous outcomes (VAS at 24, 48, and 72 hours, length of hospital stay and the total morphine consumption at 24 hours) were expressed as the weighted mean differences (WMD) with 95% CI. Variables in the meta-analysis were calculated using Stata software, version 12.0 (Stata Corp., College Station, TX). Statistical heterogeneity was evaluated using the χ^2 test and the I^2 statistic, when there was no statistical evidence of heterogeneity ($I^2 < 50\%$, $P > .1$). Consider of the multimodal local anesthesia will has potential on the VAS, we use the random-effect model to analyses the variable. Then sensitivity analysis was performed to explore the reason of heterogeneity. Subgroup analysis was conducted according to the dose of bupivacaine and spinal anesthesia. Statistical significance was set at $P < .05$ to summarize the findings across the trials.

3. Results

3.1. Search results

A total of 151 relevant articles were identified from electronic databases (Web of Science, PubMed, Embase, and Cochrane Library) according to the search strategies. Thirty-two duplicate records were removed by Endnote Software (Version X7, Thompson Reuters, CA). One hundred and eleven studies were excluded at the title and abstract level. Finally, 6 studies that compared local infiltration liposomal bupivacaine with traditional bupivacaine were included for this meta-analysis.[3,13,18–21] The baseline characteristics of the 6 included studies are summarized in Table 1. Among them, 2 studies were RCTs[13,20] and 4 studies were non-RCTs.[3,18,19,21] Five studies[3,18–21] used 20 mL (266 mg) of liposomal bupivacaine for pain control and the remaining studies[13] did not state the dose of liposomal bupivacaine. The mean age ranged from 55.1 to 71 years (Fig. 1).

3.2. Quality assessment

The quality of RCTs can be obtained in Figs. 2 and 3. Two studies did not state the random sequence generation and one study did not state the allocation concealment. The other bias were all with low risk of bias. The included 4 non-RCTs were also of high quality, according to the MINORS (21–23 points). The detailed information can be seen in Table 2.

3.3. Meta-analysis results

3.3.1. VAS at 24 hours. Data from 4 studies including 1531 hips reported the VAS at 24 hours. Compared with standard bupivacaine, liposomal bupivacaine was associated with a reduction of VAS at 24 hours (mean difference [MD] = −3.98; 95% CI, −7.29 to −0.67; $P = .018$; Fig. 4). Statistical heterogeneity was not found in VAS at 24 hours ($I^2 = 15.5\%$; $P = .314$).

Table 1

The general characteristic of the included studies.

Author	Participants		Male patients (%)		Intervention		Mean age		Outcomes	Study	Follow-up
	LB	C	LB	C	LB	C	LB	C			
Beachler et al[13]	29	40	86	72.5	NS	NS	57	57.2	4,5	RCTs	24 months
Cherian et al[18]	5267	49337	44.8	44.2	20 mL (266 mg) of LB	20 mL of 1.3% bupivacaine	64.2	64.7	4,	RCS	1 week
Domb and Gupta[19]	27	30	41	57	20 mL (266 mg) of LB	60 mL of 0.25% bupivacaine	55.5	55.8	1,2,3,4,5	CCS	72 hours
Emerson et al[20]	36	36	52.1	56.5	20 mL (266 mg) of LB	20 mL of 0.25% bupivacaine	55.1	57.4	1,5	RCTs	48 hours
Asche et al[21]	64	66	61	44	20 mL (266 mg) of LB	30 mL of 0.25% bupivacaine	67	71	1,2,4,5	RCS	48 hours
Yu et al[3]	586	686	42.8	43.3	20 mL (266 mg) of LB	40 mL of 0.25% bupivacaine	62.9	62.7	1,4	RCS	48 hours

C = standard bupivacaine, CCS = case controlled studies, LB = liposomal bupivacaine, RCT = retrospective controlled studies, RCTs = randomized controlled trials, VAS = visual analog scale, 1 = VAS at 24 hours, 2 = VAS at 48 hours, 3 = VAS at 72 hours, 4 = the length of hospital stay, 5 = total morphine consumption at 24 hours.

3.3.2. VAS at 48 hours. Data from 2 studies including 187 hips reported the VAS at 48 hours. Compared with standard bupivacaine, liposomal bupivacaine was not associated with a reduction of VAS at 48 hours (MD = −3.76; 95% CI, −9.30 to 1.77; $P = .183$; Fig. 5). Statistical heterogeneity was not found in VAS at 48 hours ($I^2 = 9.1\%$; $P = .294$).

3.3.3. VAS at 72 hours. Data from 1 study including 57 hips reported the VAS at 72 hours. Compared with standard bupivacaine, liposomal bupivacaine was not associated with a reduction of VAS at 72 hours (MD = −4.00; 95% CI, −15.16 to 7.16; $P = .483$; Fig. 6).

3.4. Total morphine consumption at 24 hours

Data from 4 studies including 328 hips reported the total morphine consumption at 24 hours. Compared with standard bupivacaine, liposomal bupivacaine was not associated with a reduction of total morphine consumption at 24 hours (MD = −3.48; 95% CI, −7.84 to 0.88; $P = .117$; Fig. 7). Statistical heterogeneity was found in total morphine consumption ($I^2 = 70.1\%$; $P = .018$).

3.5. Length of hospital stay

Data from 5 studies including 56,002 hips reported the length of hospital stay. Compared with standard bupivacaine, liposomal

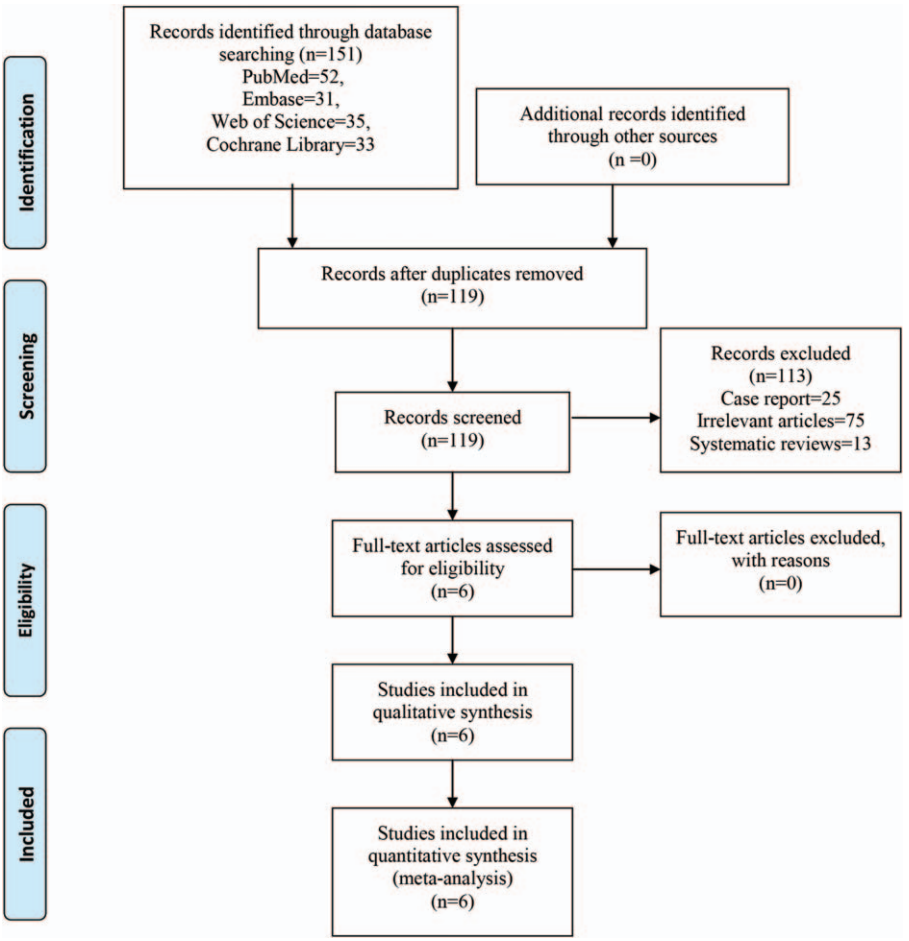

Figure 1. Flowchart of study search and inclusion criteria.

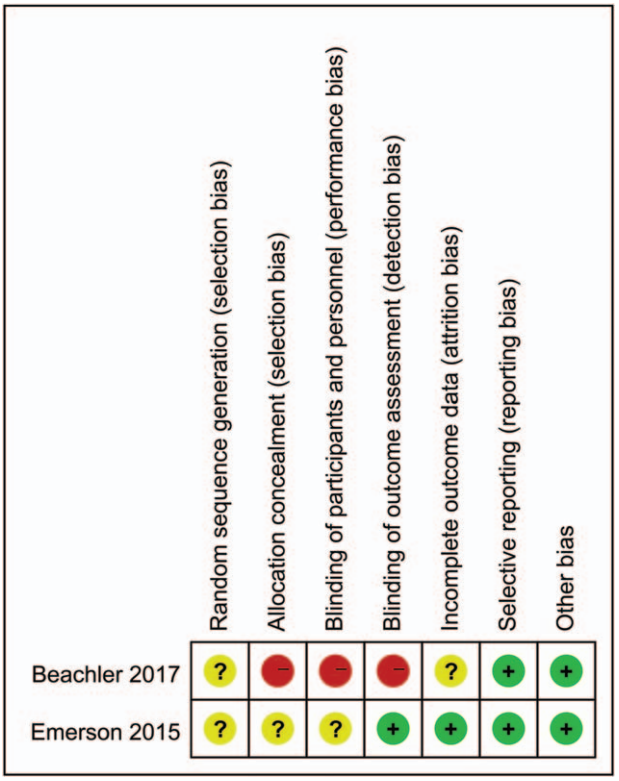

Figure 2. Risk of bias of included randomized controlled trials. +, no bias; −, bias; ?, bias unknown.

bupivacaine was associated with a reduction of length of hospital stay (MD = −0.46; 95% CI, −0.58 to −0.35; $P = .000$; Fig. 8). Statistical heterogeneity was not found in VAS at 48 hours ($I^2 = 26.2\%$; $P = .247$).

3.6. Sensitivity analysis and subgroup analysis

The sensitivity analysis results can be seen in Fig. 9. Only VAS at 24 hours and the length of hospital stay have sufficient data to perform the sensitivity analysis. Final results indicated that none of the included studies affect the final results and the results were relatively stable. Subgroup analysis results can be seen in Table 3.

4. Discussion

This is the first systematic review and meta-analysis that comparing local infiltration of liposomal bupivacaine and traditional bupivacaine for pain control in THA. We identified

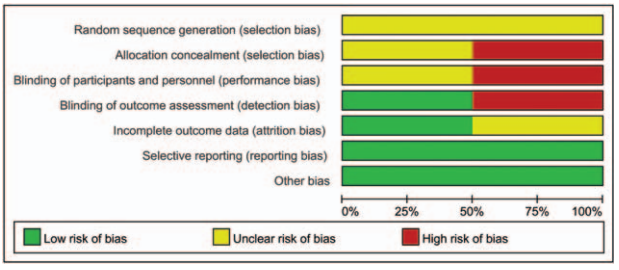

Figure 3. Risk of bias graph of the randomized controlled trials.

Table 2

The quality of the non-RCTs.

Quality assessment for non-RCT	Cherian et al[18]	Domb and Gupta[19]	Asche et al[21]	Yu et al[3]
A clearly stated aim	1	1	1	2
Inclusion of consecutive patients	1	2	1	2
Prospective of data collection	2	2	2	2
Endpoints appropriate to the aim of the study	2	2	2	2
Unbiased assessment of the study endpoint	2	2	2	2
A follow-up period appropriate to the aims of study	2	2	2	2
Less than 5% loss to follow-up	2	2	2	2
Prospective calculation of the sample size	1	1	2	1
An adequate control group	2	2	2	2
Contemporary groups	2	2	2	2
Baseline equivalence of groups	2	2	2	2
Adequate statistical analyses	2	2	2	2
Total score	21	22	22	23

RCT = randomized controlled trials.

6 studies that met inclusion criteria for this systematic review and meta-analysis. Two RCTs and 4 non-RCTs were included in this meta-analysis. Pooled results indicated that local infiltration of liposomal bupivacaine was associated with a reduction of VAS at 24 hours by 3.98 score on a 100-point VAS and length of hospital stay. There was no statistically difference between the VAS at 48 and 72 hours and total morphine consumption.

Pooled results indicated that liposomal bupivacaine was associated with a reduction of VAS at 24 hours by 3.98 score on a 100-point VAS (MD = −3.98; 95% CI, [−7.29 to −0.67]; $P = .018$). However, there was no significant difference between the VAS at 48 and 72 hours. Wu et al[22] revealed that liposomal bupivacaine can decrease the VAS score at 24 hours after TKA (MD = −0.50; 95% CI −0.97 to −0.04; $P = .034$). Another meta-analysis indicated that liposomal bupivacaine was superior than traditional bupivacaine in pain relief and morphine-sparing after TKA.[23]

Compared to traditional bupivacaine, 1 study reported a lower total morphine consumption after surgery.[19] Hamilton et al[24] conducted a meta-analysis and revealed that liposomal bupivacaine does not appear to reduce morphine consumption for all of the kinds of surgeries.

As regard to the length of hospital stay, 1 study demonstrated no improvement in the length of hospital in liposomal bupivacaine with traditional bupivacaine.[13] Another study demonstrated that liposomal bupivacaine was associated with a reduction of the length of hospital stay by 0.7 days (2.0 vs 2.7 days, $P = .002$).[21] Current meta-analysis indicated that liposomal bupivacaine was associated with a reduction of the length of hospital stay by 0.46 days (WMD = −0.46; 95% CI, −0.58 to −0.35; $P = .000$). Liu et al conducted a meta-analysis that comparing liposomal bupivacaine and femoral nerve block for knee surgery and results indicated that liposomal bupivacaine was associated with a reduction of the length of hospital stay by 0.43 days than a femoral nerve block.[25]

Another major concern was the costs of the liposomal bupivacaine for THA. Asche et al[21] revealed that the mean hospital charges were lower in the liposomal bupivacaine group ($43,794 vs $48,010; $P < .001$). However, Kuang et al[26] found

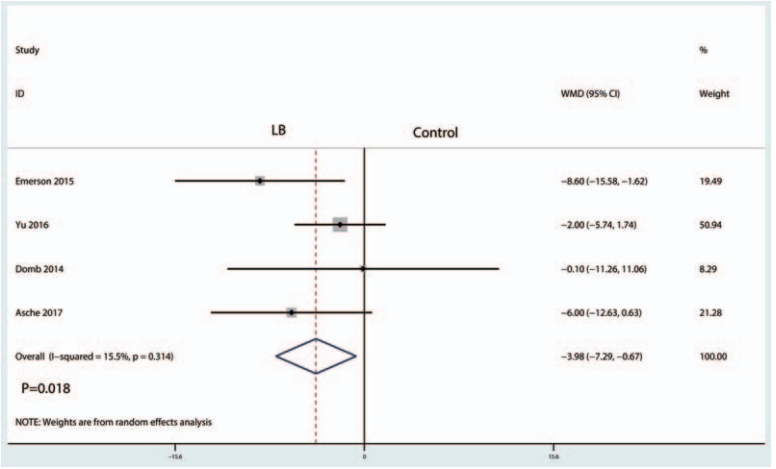

Figure 4. Forest plots of VAS at 24 hours between liposomal bupivacaine and traditional bupivacaine. VAS = visual analog scale.

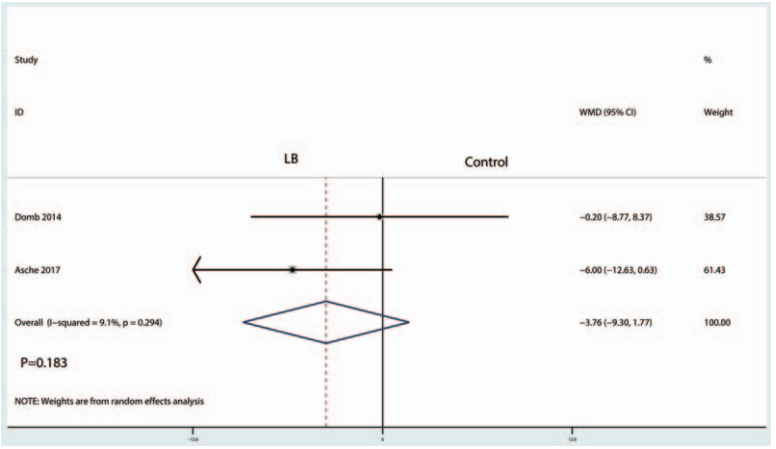

Figure 5. Forest plots of VAS at 48 hours between liposomal bupivacaine and traditional bupivacaine. VAS = visual analog scale.

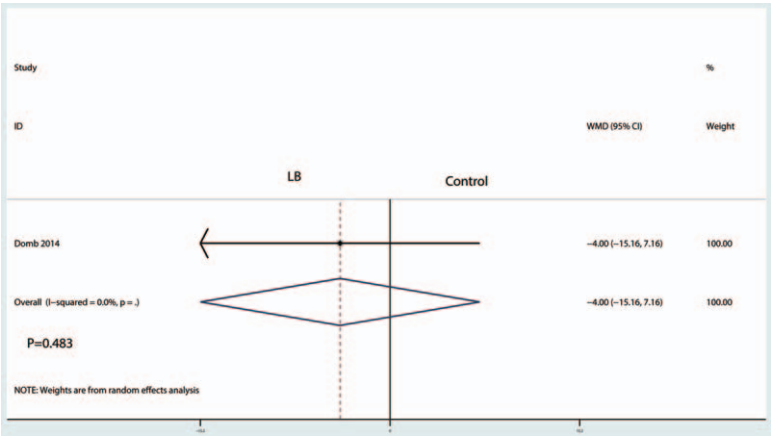

Figure 6. Forest plots of VAS at 72 hours between liposomal bupivacaine and traditional bupivacaine. VAS = visual analog scale.

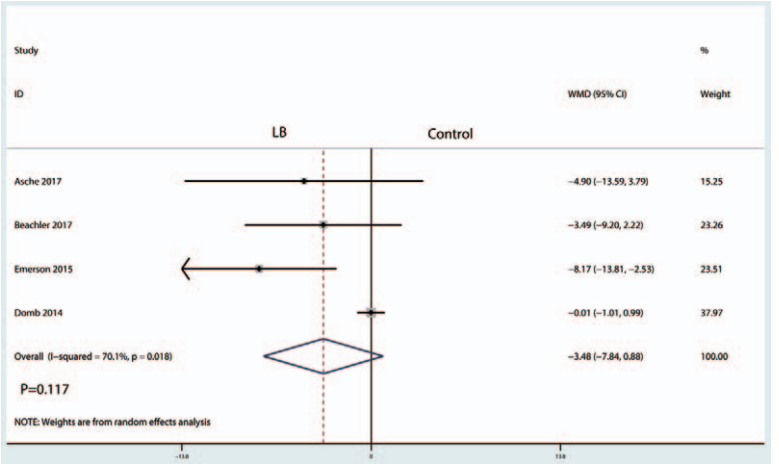

Figure 7. Forest plots of total morphine consumption at 24 hours between liposomal bupivacaine and traditional bupivacaine. VAS = visual analog scale.

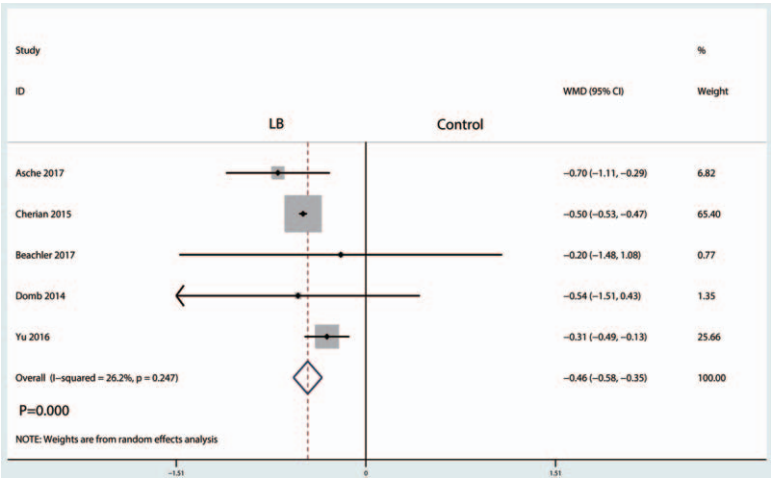

Figure 8. Forest plots of the length of hospital stay between liposomal bupivacaine and traditional bupivacaine.

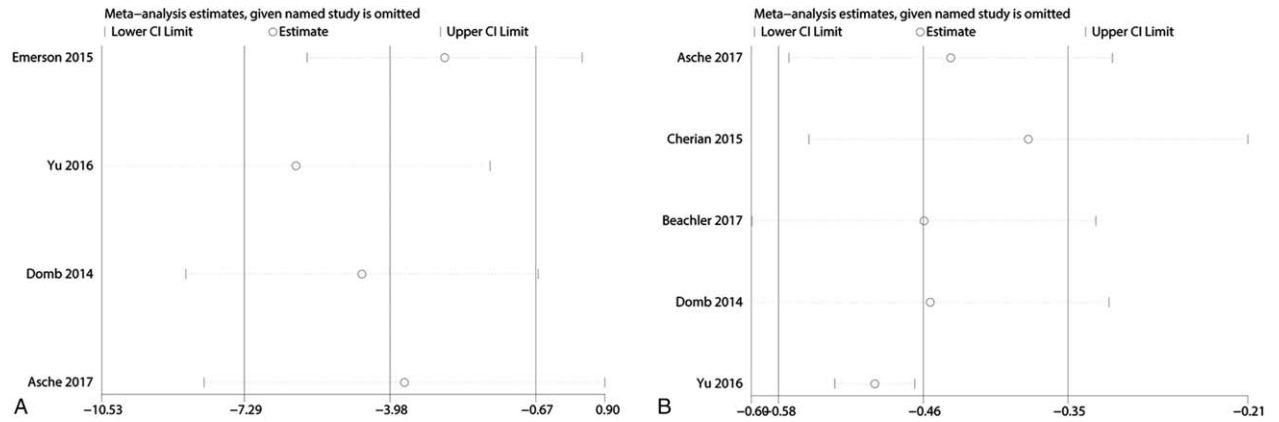

Figure 9. Sensitivity analysis of the included studies for VAS at 24 hours (A) and the length of hospital stay (B). VAS = visual analog scale.

Table 3

The subgroup analysis of the VAS at 24 hours, total morphine consumption, and the length of hospital stay.

Subgroup or Outcomes	MD (95% CI)	I^2 (%)	P
VAS at 24 hours	−3.98 (−7.29 to −0.67)	15.5	.018
Spinal anesthesia	−2.34 (−5.29 to −1.21)	23.4	.014
Liposomal bupivacaine = 226 mg	−4.01 (−8.03 to −2.56)	31.1	.021
Total morphine consumption	−3.48 (−7.84 to 0.88)	70.1	.117
Spinal anesthesia	−5.22 (−7.29 to −1.66)	58.4	.014
Liposomal bupivacaine = 226 mg	−3.88 (−6.54 to −2.16)	45.9	.036
Length of hospital stay	−0.46 (−0.58 to −0.35)	26.2	.000
Spinal anesthesia	−0.52 (−0.67 to −0.16)	15.4	.001
Liposomal bupivacaine = 226 mg	−0.38 (−0.49 to −0.22)	11.3	.000

CI = confidence interval, MD = mean difference, VAS = visual analog scale.

that liposomal bupivacaine is not worthy of being recommended as a long-acting alternative analgesic agent using the PAI method as the costs of the liposomal bupivacaine. Beachler et al[13] revealed that the cost per patient of the local injection liposomal bupivacaine was 11 times greater more than the traditional bupivacaine group. Thus, we need for more studies to identify whether administration with liposomal bupivacaine was associated with the increase of the costs.

There were several limitations to this meta-analysis: other perioperative pain management protocols were used in all of the studies, and thus heterogeneity existed in the final outcomes; the complications such as nausea, vomiting, and other complications were not reported in the included studies and thus not tested for meta-analysis; the dosage of liposomal bupivacaine was focused on the 266 mg and whether this was the optimal dose was unknown; we only identified the published papers about the liposomal bupivacaine versus traditional bupivacaine, so unpublished papers may influence the final results; and 4 non-RCTs influenced the final results due to the selective bias of the participants.

5. Conclusion

This is the first meta-analysis to compare the local infiltration anesthesia of liposomal bupivacaine versus traditional bupivacaine for the management of pain after THA. The administration of liposomal bupivacaine was associated with the reduction of VAS at 24 hours and the length of hospital stay. The optimal dose of liposomal bupivacaine will require further study. And whether administration of liposomal bupivacaine will increase the economic costs also needs more studies to identify.

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